«IT FEELS REAL TO ME»

NEURAL UNDERPINNINGS OF SUBJECTIVE REALITY IN SYNAESTHESIA AND PRESENCE

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SUMMARY

This thesis presents three different neuropsychological experiments in the context of *subjective reality,* a first experiment on synaesthesia and two investigations about presence.

Grapheme-colour synaesthetes report that they see colours when hearing spoken letters or digits and that these colours feel real to them. In order to better understand the biological basis of such perceptions, we analyzed the neuroanatomy of a group of grapheme-colour synaesthetes comparing them with a matched group of control subjects **(Experiment 1)**. Besides the traditional voxel-based morphometry method we used a newly developed method (the so-called Diffusion Tensor Imaging) to analyze neural connections via fractional anisotropy data from magnet-resonance-scans. Based on the results we suggest that colour-grapheme synaesthesia is caused by neuroanatomical differences in three different regions in the brain. Two regions are known as colour or speech processing areas (inferior frontal gyrus and occipito-temporal region) and might therefore be specific for grapheme-colour synaesthesia. The third region located in the basal ganglia, however, might also be found in other kinds of synaesthesia or similar inter-linkages between different sensory modalities.

In **Experiment 2** we tried to influence the degree of presence experienced in the virtual environment of a high-end driving simulator stimulating the dorso-lateral prefrontal cortex by means of transcranial Direct Current Stimulation. The concept of *Presence* refers to the phenomenon that the subjective location is shifted into a virtual environment and that a person behaves in this environment as if it were real. In our investigation, we measured, in addition to presence reported in a questionnaire, different parameters of driving behaviour. We found no significant influence of the brain stimulation on the reported presence. The external modulation of the brain, however, led to remarkable differences in driving behaviour. An excitation of the dorso-lateral prefrontal cortex caused a more careful driving (i.e. reduced speed, greater distance to driver ahead, less speed violations and reduced revolutions per minute). This result is

remarkable as it is one of the first proofs that external stimulation of a specific brain area can influence a multi-part behavior in a very complex and everyday-life situation.

In order to improve the paradigm used in Experiment 2 we simplified the virtual scenario and additionally registered psychophysiological measures. In **Experiment 3**, subjects were presented with a virtual rollercoaster ride. As in the previous investigation, we modulated the dorso-lateral prefrontal cortex applying a Direct Current on the scalp. Subjects were asked about their involvement in the virtual scene, answering a standard presence questionnaire. Again, the difference in the reported degree of presence did not reach significance despite a relatively high number of subjects. Psychophysiological measure (electro-dermal activity), however, significantly changed in the hypothesized direction. This result indicates that neural activity in the dorso-lateral prefrontal cortex influences the autonomic body response during the exposure to a virtual scene. We suggest that autonomic responses reflect an objective measure of the involvement in a virtual scene. Interestingly, these responses occur without changes of the conscious subjective experience and could therefore be interpreted as a kind of *low-level presence*.

Both the synaesthetes in the first experiment and the subjects in the second and third experiments reported a feeling of subjective reality. Findings of neuroanatomical differences in synaesthetes and consequences of external brain stimulation led to the hypothesis that a specific neural network in frontal and fronto-basal structures – with mainly inhibiting functions – is the biological basis of the control of the subjective feeling of reality.

ZUSAMMENFASSUNG

Diese Arbeit stellt drei neuropsychologische Untersuchungen zum Thema *Subjektive Realität* vor. Ein erstes Experiment zu Synästhesie und zwei weitere zu Präsenz.

Graphem-Farb Synästheten berichten, dass sie beim Hören von Buchstaben oder Zahlen Farben sehen. Sie sagen, dass sie diese Farben sehen, als seien sie real. Um die biologischen Ursachen von solchen Wahrnehmung besser zu verstehen, wurde in der ersten Untersuchung die Neuroanatomie von Graphem-Farb Synästheten mit jener von Kontrollpersonen verglichen **(Experiment 1)**. Neben der traditionellen Methode der Voxel-basierten Morphometrie verwendeten wir auch eine so genannte diffusionsgewichtete Imaging Methode, die es ermöglicht neuronale Verbindungen zwischen Hirnarealen zu analysieren. Sie basiert auf einer Magnetresonanz Technologie, mittels derer die fraktionale Anisotropie in Nervenzellen gemessen werden kann. Unsere Resultate zeigen, dass man die neuroanatomischen Unterschiede von Graphem-Farb Synästheten in drei Gruppen zusammenfassen kann. Zwei Gruppen von Hirngebieten sind bekannterweise involviert in Sprach- und Farbverarbeitung (inferiorer frontaler Gyrus und okzipito-temporales Übergangsgebiet). Sie sind möglicherweise spezifisch für die Graphem-Farb Synästhesie. Die dritte Gruppe von anatomischen Unterschieden liegt in den Basalganglien und könnte auch bei anderen Arten von Synästhesie oder ähnlichen Verknüpfungen von Sinnesmodalitäten auftreten.

In **Experiment 2** wurde versucht mit einer Gleichstrom-Stimulation des dorsolateralen Präfrontalkortex die erlebte Präsenz einer Versuchsperson in der virtuellen Umgebung eines Fahrsimulators zu beeinflussen. Präsenz bezeichnet das Phänomen, dass sich der subjektive Standpunkt einer Person in eine virtuelle Umgebung verschiebt und dass sie sich in dieser Umgebung verhält als wäre sie real. In unserer Untersuchung wurden sowohl das Ausmass an Präsenz mittels Fragebogen, als auch verschiedene Parameter des Fahrverhaltens erhoben. Wir fanden keine signifikanten Unterschiede in den Berichten über die erlebte Präsenz. Die externe Stimulation des Gehirns führte jedoch zu einem veränderten Fahrverhalten. Eine Erregung des dorsolateralen

Präfrontalkortex führte zu vorsichtigerem Fahrverhalten (d.h. reduzierter Geschwindigkeit, grösserem Abstand zum Vordermann, weniger Geschwindigkeitsübertretungen und geringeren Tourenzahlen). Dieses Resultat ist deshalb bemerkenswert, weil es einer der ersten Beweise ist, dass eine externe Stimulation eines spezifischen Hirnareals ein komplexes Verhalten in einer Alltagssituation beeinflussen kann.

Um das Paradigma des zweiten Experiments zu verbessern, wurde das virtuelle Szenario in **Experiment 3** vereinfacht. Zusätzlich wurden psychophysiologische Masse erhoben. Während die Versuchspersonen eine virtuelle Achterbahn sahen, wurde wie im vorigen Experiment der dorsolaterale Präfrontalkortex moduliert. Wieder zeigte die Befragung über die Präsenz der Versuchsperson in der virtuellen Umgebung keine signifikanten Effekte der Stimulation. Das psychophysiologische Mass der elektrodermalen Aktivität jedoch zeigte signifikante Unterschiede in die erwartete Richtung. Wir konnten zeigen, dass die Aktivität des Präfrontalkortex die autonome Körperreaktion während dem Erleben eines virtuellen Szenarios beeinflusst. Interessanterweise treten diese Reaktionen auf ohne Veränderungen des bewussten subjektiven Erlebens. Man könnte sie deshalb als eine Art automatischer low-level Präsenz interpretieren.

Sowohl Synästheten als auch die Versuchspersonen im zweiten und dritten Experiment berichten ein Gefühl von subjektiver Realität. Die neuronalen Grundlagen dieses Gefühls könnten – ausgehend von den Erkenntnissen aus diesen Experimenten – in frontalen und fronto-basalen Hirnstrukturen mit hauptsächlich hemmender Funktion liegen.

INTRODUCTION

1.1. «It feels real to me»

Consciousness has been a central concern of neuroscience for a long time. There have been attempts to find the neural correlates of consciousness in different regions of the brain (Crick & Koch, 2005) and to do through a variety of different approaches (Tononi & Edelman, 1998). "How does the brain integrate sensory input into one perception?", "What are the neural foundations of the experience of reality?" are questions neuroscientist try to answer. Despite the many attempts to do so, we are still far from discovering the causes of consciousness at a neural level. This thesis tries to take some small steps in this direction, by investigating the neural correlates of synaesthesia and presence.

The fascinating perceptual phenomenon of synaesthesia is in the focus-point of the first experiment. Synaesthesia means a perception of a stimulus through more than one sensory modality. People with this ability report, for instance, that they see a colour when hearing a word. This colour feels real to them even if there is no actual coloured object eliciting their colour experience. We try to find neuroanatomical differences in these synaesthetes using a combination of new and traditional neuroimaging techniques.

In the second and third experiment, the feeling of reality is investigated in a virtual environment. A virtual environment (VE) makes it possible to gradually modulate the felt reality of the perceived surrounding, and therefore affords great new possibility to investigate the neural correlates of the perception of reality. In our experiments we try to modulate the feeling of reality by external stimulation of the brain. In experiment 2 the VE consists of a driving-simulator, while experiment 3 uses a virtual roller-coaster ride.

ANALYZING BRAIN ANATOMY

This section gives a short introduction into the methods used in Experiment 1. The principles of voxel-based morphometry and diffusion tensor imaging are explained. Details of the analyses are described in Section 4.5.

2.1. Classical Brain Morphometry

The traditional way of analyzing brain anatomy is normally through a visual inspection of structural brain scans. A certain volume is calculated after a manual segmentation of the brain tissue. This method has the disadvantage that it requires a good knowledge about brain anatomy and its validity is undermined by a suboptimal inter-rater reliability. As a result, automated analyses, such as the Deformation-based Morphometry (DBV) and the Voxel-based Morphometry (VBM), have been developed. As VBM was used in Experiment 1 of this thesis it shall now be presented here in more detail.

2.2. Voxel-based Morphometry (VBM)

Voxel-based morphometry (VBM) (Ashburner, Friston 2000) is an automated method for analyzing and quantifying brain anatomy. It used anatomical brain scans (T1-weighted images) from structural Magnetic Resonance Imaging (sMRI). In a first step, the individual brain images are linearly normalized in order to allow for a comparison of different brains. As non-linear normalization is not used, individual anatomical differences are conserved. Secondly, the spatially normalized images are segmented into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF). The following step includes a smoothing of the segmented brain tissue using a Gaussian kernel. The smoothing makes it possible to use a voxel-by-voxel analysis as each voxel now contains an average concentration from its surrounding. Moreover, the smoothing leads to more normally distributed data, increasing the validity of parametric statistical test. The subsequent statistical analysis uses the general linear model (GLM). Standard parametric statistical test (normally t-tests) are used to quantify an effect under study. Because of the huge number of tests, it is necessary to correct for multiple comparisons.

2.3. Diffusion Tensor Imaging (DTI)

Besides methods of morphometrical analyses of the brain, there is a newly developed method for analyzing another aspect of brain anatomy. The Diffusion Tensor Imaging (DTI) method is based on diffusion weighted brain scans. This extension of the traditional MRI technique is based on the anisotropic characteristic of water in a tissue; i.e. water does not diffuse in all directions in the same amount. Axons in nerve bundles and – more specifically – their myelin sheaths facilitate the diffusion of water molecules along the direction of the nerve bundles. Therefore, the direction of the diffusion of the water molecules can be used as an indirect measure of neural connections.

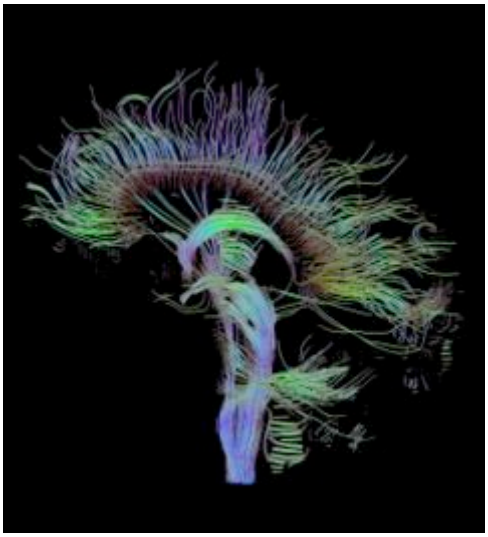

Figure 1: Visualization of brain fibres with DTI and tractography

The diffusion-weighted MR-scan applies different diffusion gradients using variations in the magnetic field. Normally, a number of gradients between 6 and 30 is used. Based on these gradients it is possible to calculate a diffusion tensor for each voxel indicating the main direction of a neural fibre from or through a voxel. These tensors can be used for brain tractography (visualization of brain fibres). Moreover, it is possible to test statistically differences of anisotropy. Significant statistical differences are normally interpreted as stronger or weaker neural connections. By allowing an analysis of neural connections on an anatomical level, DTI thus forms an interesting methodological supplement to the traditional VBM analysis of brain anatomy.

SYNAESTHESIA

This section introduces the perceptual phenomenon of synaesthesia, the focus of the first experiment. After a description of the characteristics of synaesthesia and an overview of the current knowledge we will describe the relation and the importance of synaesthesia for the investigation of subjective reality.

3.1. Synaesthesia – a perceptual phenomenon

The word *synaesthesia* derives from the Greek pre-syllable *syn* (together) and *aisthesis* (sensation); and denotes the perceptual phenomenon whereby a unimodal stimulation leads to a perception in more than one sensory modality. For example, when hearing a word, a certain synaesthete also sees colours in front of her eyes. Experiences similar to synaesthesia have been reported after drug-use (Shanon, 2002) indicating a possible ability for synaesthetic sensations in every person.

Synaesthetes, however, experience the combination of sensory modalities at all time (criterion of constancy) and a certain stimulus always evokes the same sensation (criterion of consistency) (Asher, Aitken, Farooqi, Kurmani, & Baron-Cohen, 2006). Moreover, synaesthetes report that they have had their sensations for as long as they can remember. Synaesthetic experiences cannot be evoked or controlled at will.

Synaesthesia is idiosyncratic, i.e. two synaesthetes (even siblings) never report the same combination of evoking and concurrent (synaesthetic) perception. There are different frequencies of combinations of evoking and concurrent modalities (see Robertson & Sagiv, 2005), the most frequent however, is the coloured perception of letters and words called *grapheme-colour-synaesthesia*. Remarkably, eighty-nine percent of the concurrent perceptions are sensations of colour.

The prevalence of synaesthesia varies in different investigations from 1:25’000 (Cytowic, 1989) to 1:2’000 (Baron-Cohen, Burt, Smith-Laittan, Harrison, & Bolton, 1996) and is higher in women (from 3:1 to 6:1). Synaesthesia is partially genetically determined (Smilek et al., 2002); recent reports, however, show that learning can influence synaesthesia (Beeli, Esslen, & Jäncke, 2007).

3.2. Behavioural differences in synaesthetes

3.2.1. Adapted Stroop-tasks

The Stroop-effect describes the phenomenon that reaction times of naming a font colour of a word are not independent of the content of the word. In the standard task described by Stroop (1935), participants are asked to name the ink colour of a printed word. If the ink colour is incongruent with the meaning of the word (e.g. the word *red* printed in blue, see Figure 2), participants need more time for the naming task compared to conditions where the ink is congruent with the meaning of the word.

Figure 2: Example of the incongruent condition in the original Stroop-task.

The Stroop-task has been adapted in different experiments in the context of research about synaesthesia. In word-colour synaesthetes, the ink colour of the word not only conflicts with the meaning of the word but also with the synaesthetic colour elicited by the word. Naming time is enhanced if the synaesthetic colour is incongruent with the ink colour and faster in congruent conditions (Dixon, Smilek, Cudahy, & Merikle, 2000).

The principle of the Stroop task was used also in our previous investigation about synaesthesia evaluating a unique case of musical interval-taste synaesthesia (Beeli, Esslen, & Jancke, 2005).

3.2.2. Pop-out

Behavioural differences in synaesthetes have been found not only in adapted Stroop-tasks, but also in so-called *pop-out tasks.* Ramachandran & Hubbard (2001) presented the square shown in Figure 3 to synaesthetes and found an advantage in reaction times in naming the form built by certain letters (in the example a triangle).

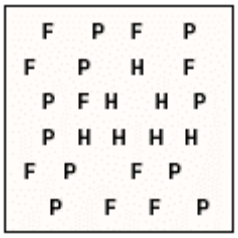

Figure 3: Task used in the experiment by Ramachandran & Hubbard (2001). Which form is built by the Hs?

3.3. Neural correlates of synaesthesia

One of the first experiments investigating the neural correlates of synaesthesia was performed by Paulesu et al. (Paulesu et al., 1995). Six grapheme-colour synaesthetes were presented with tones and spoken words while the neural activation was registered using Positron-Emission-Tomography (PET). The perception of words led to enhanced neural activity in synaesthetes in frontal brain areas (middle and inferior frontal gyrus and insula), in the superior temporal gyrus and in the left parieto-occipital junction. Activation differences in the posterior part of the inferior temporal gyrus were also found. Against the authors' expectation, no differences were detected in early visual areas.

Based on this study, Nunn et al. (2002) used a similar paradigm but a different method. In the functional Magnetic Resonance Imaging (fMRI) they found activation differences in synaesthetes (listening to words) in early visual areas (V4), predominantly in the left hemisphere. This area has been found to be activated during colour perception and is often referred to as the *colour centre* of the brain. Similar results were found by Hubbard & Ramachandran (2005).

Neural correlates of the grapheme-colour synaesthesia were also investigated with Electroencephalography (EEG). An investigation by Schiltz et al. (1999) used an *oddball-paradigm*. The classical P300 reaction was enhanced in synaesthetes, especially in frontal electrodes. The paradigm used by Nunn et al. (2002) was transferred in an EEG-experiment using an auditory presentation of letters and words and comparing brain activations of grapheme-colour synaesthetes with non-synaesthetic controls (Beeli, Esslen, & Jancke, 2007). This investigation could replicate the finding of different

previous studies. First, there were activation differences in occipito-temporal regions, and also in areas of colour perception. Secondly, there were additional activation differences in frontal and parietal areas. For a detailed discussion see Beeli et al. (2007).

Besides functional brain differences in synaesthetes there is recent evidence that synaesthesia also has an anatomical basis. Rouw & Scholte (2007) have shown that there is a stronger fractional anisotropy in the left occipito-temporal region in synaesthetes, indicating an enhanced neural wiring in their brains.

3.3.1. Summary

Different neuroimaging methods have found a neural basis of synaesthesia. The results obtained from their employment differ in some respects. There is one main correspondence, however, in the localization of the neural basis of synaesthesia in the occipito-temporal region (PIT and V4) in the left hemisphere. There are recent investigations into the anatomical correlates of synaesthesia using the newly developed methods of Diffusion Tensor Imaging (DTI). Interestingly, the traditional anatomical analysis of synaesthetes' brains has not been performed, and shall therefore be the main focus of Experiment 1 in this thesis.

3.4. Synaesthesia and subjective reality

One interesting characteristic of synaesthetic perceptions is that they appear to synaesthetes as if they were real. Synaesthetes report that they know that the colour of a letter, for instance, is different from its ink colour but, nevertheless, it feels real to them. This distinguishes a synaesthetic perception from mere mental imagery. It has been shown that synaesthetic perceptions do not share the same neural networks as mental imagery (Rich et al., 2006). Synaesthesia renders possible the investigation of neural correlates of consciousness without a direct (but only indirect) sensory input, and can therefore have a great impact on the quest for the neural correlates of consciousness.

EXPERIMENT 1

The neuroanatomical basis of grapheme-colour synaesthesia

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4.1. Abstract

People with synaesthetic ability perceive certain stimuli in more than one sensory modality. For example, when hearing a word a grapheme-colour synaesthete also sees a colour. There are different types of linkages between sensory modalities, the most frequent however is the coloured perception of graphemes. Different neuroimaging studies have provided some evidence for a neural basis of this type of synaesthesia. The present study reports the first complete neuroanatomical analysis of synaesthetes' brain, comparing neural connectivity and grey and white matter volumes with non-synaesthetic controls. Surprisingly, we identified different groups of clusters of anatomical differences in synaesthetes that are well in line with earlier findings of activation differences. We therefore suggest that synaesthesia has also a neural foundation at an anatomical level.

4.2. Introduction

There has been a rapid increase in the number of scientific research about synaesthesia lately. Different attempts have been made to better understand the phenomenon of the inter-linkage between different sensory modalities occurring in synaesthesia. Besides synaesthetes' descriptive reports of subjective experience there is evidence that synaesthetes show different behaviors in specific behavioral tests (Rich and Mattingley, 2002). While there is some controversy as to whether synaesthesia is determined by genetic factors (Baron-Cohen et al., 1996; Smilek et al., 2005), there is certainly evidence that the specific inter-linkage (e.g. which number has which colour) must be learned (Beeli et al., 2007b; Simner, 2007). There are many possible combinations of intermodal linkage in synaesthesia, some of which are very specific, for instance musical intervals evoking a taste perception (Beeli et al., 2005). But the most common is the coloured perception of letters/words or numbers (graphemes), this so-called grapheme-colour synaesthesia therefore, attracting the interest of most synaesthesia research groups.

Numerous investigations have demonstrated a neuronal basis for synaesthesia. In neuroimaging experiments, especially with functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), specific brain areas have been found that show different activations in synaesthetes compared with controls (Hubbard et al.,

2005; Nunn et al., 2002; Paulesu et al., 1995; Rich and Mattingley, 2002; Sperling et al., 2006; Weiss et al., 2005). The regions are the left and right colour centre (V4), adjacent areas of the posterior inferior temporal gyrus (PIT) and lingual gyrus, frontal brain areas, and regions in the right parietal cortex (IPS, intraparietal sulcus) (for an overview see Beeli et al., 2007a). An inhibition of the right parietal cortex with transcranial magnetic stimulation (TMS) can disrupt synaesthesia temporarily (Esterman et al., 2006). An alternative method, the electroencephalography (EEG), also revealed different activations in synaesthetes in this brain region (Beeli et al., 2007a), further supporting the idea of a neural underpinning of synaesthesia.

A very recent investigation (Rouw and Scholte, 2007) using diffusion tensor imaging (DTI), a newly developed extension of the traditional MRI methods, provides the first evidence that the different activations are reflected also at an anatomical level. To our knowledge, there have been no investigations about anatomical differences in synaesthetes using the traditional method of structural magnetic resonance imaging (sMRI) based on T1-weighted MR scans.

In the present study we therefore sought to replicate the recent findings by Rouw & Scholte (2007) and to extend these finding by utilizing additional methods with which to analyze the brain anatomy of synaesthetes. This was achieved by comparing volumes of grey and white brain matter of synaesthetes with non-synaesthetic controls. We hypothesized anatomical differences, especially in the occipito-temporal brain region in the left hemisphere.

4.3. Results

Figure 1 shows significantly increased grey matter (GM) volumes, white matter (WM) volumes and higher fractional anisotropy (FA) in synaesthetes. Figure 2 shows the inversed contrast (controls > synaesthetes).

4.3.1. Grey matter (GM) volume differences

Synaesthetes have increased GM volumes in the left occipito-temporal region (lingual gyrus and fusiform gyrus) and in right inferior frontal gyrus (pars triangularis and pars opercularis) (Fig. 1, red). Reduced GM volumes were found in the putamen in

both hemispheres (Fig. 2, red). In the left hemisphere, the GM volume differences reach into the adjacent area of the insula and in the right hemisphere into the pallidum (Fig. 2, red).

4.3.2. White matter (WM) volume differences

As there are no labels for all WM structures, we indicate the nearest GM areas for the localization of structural differences. In the left hemisphere, synaesthetes have increased WM volumes between the calcarine sulcus and the lingual gyrus and under the posterior part of the middle temporal gyrus. In the right hemisphere, the posterior insula has an increased WM volume (Fig. 1, blue).

Controls show increased WM volume under the left superior frontal gyrus, the left superior temporal gyrus, the left fusiform gyrus, the left lingual gyrus and the right inferior frontal gyrus. It is remarkable that in nearly all these areas, synaesthetes have increased GM volumes.

4.3.3. Fractional anisotropy (FA)

Synaesthetes have higher FA in a tract reaching from left parietal areas down through the left posterior cingulate cortex to an area between the left fusiform gyrus and the left posterior middle temporal gyrus and under the left middle frontal gyrus (Fig. 1, green).

Controls, however, have higher FA between the pallidum, the putamen and the caudate nucleus (Fig. 2, green).

Details of the areas with MNI coordinates are shown in table 1 (Supplementary Information).

4.3.4. Results summary

Taken together, the results in the different analyses can be grouped in three major clusters of brain regions.

(1) The smallest cluster is located in the right inferior frontal gyrus (the Broca's homologue area). In this region, synaesthetes have increased grey matter volumes and controls increased white matter volumes.

(2) The second cluster is constituted by group differences in the basal ganglia. Mainly, there are increased grey matter volumes in controls in the putamen and adjacent regions. Controls also consistently show increased FA between putamen, the pallidum and the caudate nucleus.

(3) The most prominent and recurrent cluster results from GM, WM and FA-analyses and is located in the occipito-temporal junction exclusively in the left hemisphere (including posterior temporal regions, fusiform and lingual gyrus reaching into parietal and occipital regions). Regions inside this cluster show increased grey matter volumes and increased connectivity in synaesthetes; controls, on the other hand, have increased white matter volumes.

4.4. Discussion

The present study investigates anatomical differences in grapheme-colour-synaesthetes. Interestingly, a good correspondence was found between GM volume and WM volume differences such that when synaesthetes have an increased GM volume in fusiform gyrus controls have a higher WM volume. This principle applies not only to the left fusiform gyrus but also to the left lingual gyrus, the right insula and the right inferior frontal gyrus. This finding suggests that grey matter volumes might be increased at the cost of white matter volumes. Of course, fractional anisotropy does not directly depend on volume differences from VBM data, but the FA differences found are located in adjacent brain structures and might therefore still be associated functionally with the volume differences.

The first cluster of group differences located in the right inferior frontal gyrus (IFG, BA 44), in which synaesthetes show increased GM volumes, might be the anatomical basis of activation differences found in fMRI and EEG (electroencephalogram) studies of grapheme-colour-synaesthesia (Beeli et al., 2007a; Schiltz et al., 1999; Sperling et al., 2006). This brain area is known to be activated during semantic encoding (Dapretto and Bookheimer, 1999), especially during implicit elaboration (Kang et al., 1999). A specific colour-perception of graphemes requires semantic encoding. As synaesthetic perceptions are implicit and automatic, implicit semantic elaboration might be more efficient in

synaesthetes compared with non-synaesthetes as a consequence of increased GM volumes in IFG.

The second cluster showing decreased grey matter volumes and neural connectivity in synaesthetes is located in the core regions of the basal ganglia. These brain structures are known to have modulating influence on cortical activity, particularly in the motor system. This modulation is mainly inhibitory and mediated through the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in the striatum and the pallidum (Hikosaka et al., 2007). There is also evidence that the basal ganglia are involved in learning processes (Brown et al., 2006). The putamen has been found to be specifically activated in a task were a stimulus-response linkage has to be changed (Parris et al., 2007). The anatomical differences in synaesthetes in this brain region might explain the very constant linkage between a specific grapheme and a particular colour. One could assume that a reduced GM volume leads to a decreased ability of stimulus-response linkage modulation and to a persistent linkage even through different sensory modalities. An alternative explanation of the anatomical differences is a reduced inhibition of the thalamus by the putamen leading to an increased activation in different cortical areas. This phenomenon called "disinhibition" has been postulated in the theory by Grossenbacher & Lovelace (2001) as the origin of synaesthesia. There are also reports that drugs can elicit synaesthesia (Shanon, 2002). Similarly, these experiences might be explained as an effect of disinhibition of the drugs on the thalamus.

The third cluster is located in the left occipito-temporal brain region. This result is highly consistent with many earlier findings reporting activation differences in this area with different methods (Beeli et al., 2007a; Hubbard et al., 2005; Nunn et al., 2002; Paulesu et al., 1995; Sperling et al., 2006) and is also in line with the finding by Rouw & Scholte (2007). The increased GM volumes in the colour processing areas (fusiform gyrus) and the adjacent area of the lingual gyrus are the first findings of morphometric anatomical differences in areas that have been postulated to form the neural basis of the coloured perception of the graphemes.

Based on current understanding about the functions of the identified areas, we propose that the differences in IFG reflect the processing of graphemes, while the involvement of the occipito-temporal junction can be attributed to the processing of

colour. These areas may therefore be specific to grapheme-colour synaesthesia. On the other hand, the differences in the basal ganglia might be independent of the kind of synaesthesia. It remains to be shown which of the anatomical differences are critically involved in the occurrence of synaesthesia and which form a sufficient condition of synaesthesia.

In summary, our results confirm earlier investigations with findings of activation differences in grapheme-colour synaesthetes. Especially, the main cluster identified in this study located in the occipito-temporal junction is well in line with earlier reports. Nevertheless, the minor clusters can also be understood in the context of the findings from functional brain imaging studies. Altogether, we can confirm an anatomical basis for grapheme-colour synaesthesia that is not simply based on increased neural connectivity – as proposed in some theories (Hubbard and Ramachandran, 2005) – but is also associated with grey and white matter volume differences. This finding means that existing theories about the neural basis of synaesthesia need to be revised accordingly and developed further on the basis of this revision. Importantly, it must be explained whether these GM and WM volume differences and the differences in FA are genetically determined or caused by environmental influences.

4.5. Methods

4.5.1. Subjects:

14 synaesthetes (10 women and 4 men) with a mean age of 29.3 years (SD: 10.3) and 14 controls matched for age, sex and education participated in the study. All synaesthetes reported lifelong history of ‘‘colour-hearing’’ perception (i.e. as long as they could remember) and were tested carefully for their colour perception to letters and number with the established ‘‘test of genuineness’’ that is typically used for diagnosis of synaesthesia (Baron-Cohen et al., 1987). All synaesthetes had to repeat this test at least one month later, and all demonstrated constant synaesthetic perception. All participants where right handed (Annett, 1970), had no history of neurological or psychiatric disease, and all gave their informed consent.

4.5.2. MRI data acquisition:

Magnetic Resonance Imaging (MRI) scans were acquired on a 3.0 T Philips Intera whole body scanner (Philips Medical Systems, Best, The Nederlands) equipped with a transmit-receive body coil and a commercial eight-element sensitivity encoding (SENSE) head coil array.

4.5.2.1. T1-weighted MRI scans:

A volumetric 3D T1-weighted gradient echo sequence (TFE, turbo field echo) scan was obtained with a measured spatial resolution of 1x1x1.5 mm^3 (acquisition matrix 224x224 pixels, 180 sclices) and a reconstructed resolution of 0.86x0.86x0.75 mm^3 (reconstructed matrix 256x256 pixels, 180 slices). Further imaging parameters were: Field of view FOV = 220x220 mm^2, echo-time TE = 2.3 ms, repetition-time TR = 20 ms, flip-angle FA = 20°.

4.5.2.2. Diffusion-weighted MRI scans:

As one aim of this study was the replication of the findings on structural connectivity by Rouw & Scholte (2007), we adhered as closely as possible to their analysis. Structural connectivity was based on the fractional anisotropy (FA), which was calculated on the basis of diffusion-weighted spin-echo echo-planar imaging (EPI) measurements (TR 10,166 ms, TE 50 ms, flip angle 90°, FOV 200 x 200 mm, measured spatial resolution of 2.08x2.13x2.0 mm^3, matrix size 96 x 96, 50 slices, slice thickness 2 mm, reconstructed voxelsize 1.56 x 1.56 x 2 mm^3, reconstructed matrix 128x128 pixels, 50 slices, SENSE factor 2.1. Diffusion was measured in 15 noncollinear directions followed by a non-diffusion-weighted volume (reference volume). Total acquisition time was 15 min.

4.5.2.3. Construction of customized a priori maps:

In order to account for the preponderance of females in our study we used customized a priori maps for spatial normalization and tissue class segmentation. In a first run steps 1-4 (see below) were realized using the canonical T1-weighted ICBM 452 template (International Consortium for Brain Mapping; http://www.loni.ucla.edu /ICBM/). The resulting normalized grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) segments were averaged separately in order to obtain customized a priori maps of each tissue class.

4.5.2.4. Imaging data preprocessing and statistical analysis:

For the analysis of grey (GM) and white matter (WM) volumes we applied the voxel-based morphometry (VBM) (Ashburner and Friston, 2000) implemented in the VBM5 toolbox (http://dbm.neuro.uni-jena.de/vbm/) for the statistical parametric mapping (SPM5) software (http://www.fil.ion.ucl.ac.uk/spm/). The following steps were realized: 1) The coordinate origin was manually set on the anterior commissure. 2) Intensity inhomogeneity (bias field) correction, tissue class segmentation, and spatial normalization (affine and warping) was done using the unified segmentation approach (Ashburner and Friston, 2005) with customized a priori maps. 3) To investigate absolute volumes, Jacobian modulation was applied to the deformation fields. 4) To enhance tissue class segmentation, Hidden Markov Random Field (HMRF) modulation was applied (Cuadra et al., 2005). 5) GM and WM images were smoothed with a Gaussian kernel of FWHM = 8 mm. 6) We used the general linear model (GLM) implemented in SPM5 to analyze GM and WM volume differences between synaesthetes and control subjects. In GM and WM analysis, total GM volume (TGMV) and total WM volume (TWMV) were used as a covariate of no interest, respectively. Because we had a priori hypotheses, we used a statistical height threshold of $p < 0.001$ (uncorrected for multiple comparisons) and an extend threshold of 120 voxels.

4.5.2.5. Analysis of fractional anisotropy (FA):

Here we applied parts of the preprocessing stream of Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006) using FSL (Smith et al., 2004) / FDT (Behrens et al., 2003) tools implemented in the FMRIB Software Library (http://www.fmrib.ox.ac.uk/fsl/) to create Fractional Anisotropy (FA) maps. The following steps were realized: 1) Eddy current correction was applied using FDT. 2) Tensors were fitted to the data using TBSS. 3) Voxelwise statistical analysis of the FA data was carried out using FSL. 4) A mean FA image was created after alignment into common stereotactic space and was then reduced to an image called “mean FA skeleton” (an alignment-invariant tract representation) helping to overcome the problem of the arbitrariness of smoothing-extent. 5) The significance of the comparison between the two groups was calculated by means of permutation testing.

4.6. References

Annett, M.A. (1970). A classification of hand preference by association analysis. British Journal of Psychology *61*, 303-321.

Ashburner, J., and Friston, K.J. (2000). Voxel-Based Morphometry--The Methods. NeuroImage *11*, 805-821.

Ashburner, J., and Friston, K.J. (2005). Unified segmentation. NeuroImage *26*, 839-851.

Baron-Cohen, S., Burt, L., Smith-Laittan, F., Harrison, J., and Bolton, P. (1996). Synaesthesia: prevalence and familiality. Perception *25*, 1073-1079.

Baron-Cohen, S., Wyke, M.A., and Binnie, C. (1987). Hearing words and seeing colours: an experimental investigation of a case of synaesthesia. Perception *16*, 761-767.

Beeli, G., Esslen, M., and Jancke, L. (2005). Synaesthesia: when coloured sounds taste sweet. Nature *434*, 38.

Beeli, G., Esslen, M., and Jancke, L. (2007a). Time Course of Neural Activity Correlated with Colored-Hearing Synesthesia. Cereb. Cortex.

Beeli, G., Esslen, M., and Jäncke, L. (2007b). Frequency Correlates in Grapheme-Color Synaesthesia. Psychological Science *18*, 5.

Behrens, T.E.J., Woolrich, M.W., Jenkinson, M., Johansen-Berg, H., Nunes, R.G., Clare, S., Matthews, P.M., Brady, J.M., and Smith, S.M. (2003). Characterization and propagation of uncertainty in diffusion-weighted MR imaging. Magnetic Resonance in Medicine *50*, 1077-1088.

Brown, P., Chen, C.C., Wang, S., Kuhn, A.A., Doyle, L., Yarrow, K., Nuttin, B., Stein, J., and Aziz, T. (2006). Involvement of Human Basal Ganglia In Offline Feedback Control of Voluntary Movement. Current Biology *16*, 2129-2134.

Cuadra, M.B., Cammoun, L., Butz, T., Cuisenaire, O., and Thiran, J.P. (2005). Comparison and validation of tissue modelization and statistical classification methods in T1-weighted MR brain images. Medical Imaging, IEEE Transactions on *24*, 1548-1565.

Dapretto, M., and Bookheimer, S.Y. (1999). Form and Content: Dissociating Syntax and Semantics in Sentence Comprehension. Neuron *24*, 427-432.

Esterman, M., Verstynen, T., Ivry, R.B., and Robertson, L.C. (2006). Coming Unbound: Disrupting Automatic Integration of Synesthetic Color and Graphemes by Transcranial Magnetic Stimulation of the Right Parietal Lobe. Journal of Cognitive Neuroscience *18*, 1570-1576.

Grossenbacher, P.G., and Lovelace, C.T. (2001). Mechanisms of synesthesia: cognitive and physiological constraints. Trends in Cognitive Sciences *5*, 36-41.

Hikosaka, O., Tepper, J.M., Abercrombie, E.D., and Bolam, J.P. (2007). GABAergic output of the basal ganglia. In Progress in Brain Research (Elsevier), pp. 209-226.

Hubbard, E.M., Arman, A.C., Ramachandran, V.S., and Boynton, G.M. (2005). Individual differences among grapheme-color synesthetes: brain-behavior correlations. Neuron *45*, 975-985.

Hubbard, E.M., and Ramachandran, V.S. (2005). Neurocognitive Mechanisms of Synesthesia. Neuron *48*, 509-520.

Kang, A.M., Constable, R.T., Gore, J.C., and Avrutin, S. (1999). An Event-Related fMRI Study of Implicit Phrase-Level Syntactic and Semantic Processing. NeuroImage *10*, 555-561.

Nunn, J.A., Gregory, L.J., Brammer, M., Williams, S.C., Parslow, D.M., Morgan, M.J., Morris, R.G., Bullmore, E.T., Baron-Cohen, S., and Gray, J.A. (2002). Functional magnetic resonance imaging of synesthesia: activation of V4/V8 by spoken words. Nat. Neurosci. *5*, 371-375.

Parris, B.A., Thai, N.J., Benattayallah, A., Summers, I.R., and Hodgson, T.L. (2007). The Role of the Lateral Prefrontal Cortex and Anterior Cingulate in Stimulus-Response Association Reversals. Journal of Cognitive Neuroscience *19*, 13-24.

Paulesu, E., Harrison, J., Baron-Cohen, S., Watson, J.D., Goldstein, L., Heather, J., Frackowiak, R.S., and Frith, C.D. (1995). The physiology of coloured hearing. A PET activation study of colour-word synaesthesia. Brain *118*, 661-676.

Rich, A.N., and Mattingley, J.B. (2002). Anomalous perception in synaesthesia: a cognitive neuroscience perspective. Nat.Rev.Neurosci. *3*, 43-52.

Rouw, R., and Scholte, H.S. (2007). Increased structural connectivity in grapheme-color synesthesia. Nat Neurosci *10*, 792-797.

Schiltz, K., Trocha, K., Wieringa, B.M., Emrich, H.M., Johannes, S., and Munte, T.F. (1999). Neurophysiological aspects of synesthetic experience. J.Neuropsychiatry Clin.Neurosci. *11*, 58-65.

Shanon, B. (2002). Ayahuasca visualizations: A structural typology. Journal of Consciousness Studies *9*, 3-30.

Simner, J. (2007). Beyond perception: synaesthesia as a psycholinguistic phenomenon. Trends in Cognitive Sciences *11*, 23-29.

Smilek, D., Dixon, M.J., and Merikle, P.M. (2005). Synaesthesia: Discordant male monozygotic twins. Neurocase *11*, 363-370.

Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, C.E., Watkins, K.E., Ciccarelli, O., Cader, M.Z., Matthews, P.M., and Behrens, T.E.J. (2006). Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. NeuroImage *31*, 1487-1505.

Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E.J., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E*., et al.* (2004). Advances in functional and structural MR image analysis and implementation as FSL. NeuroImage *23*, S208-S219.

Sperling, J.M., Prvulovic, D., Linden, D.E., Singer, W., and Stirn, A. (2006). Neuronal correlates of colour-graphemic synaesthesia: a fMRI study. Cortex *42*, 295-303.

Weiss, P.H., Zilles, K., and Fink, G.R. (2005). When visual perception causes feeling: Enhanced cross-modal processing in grapheme-color synesthesia. NeuroImage *28*, 859-868.

4.7. Figures

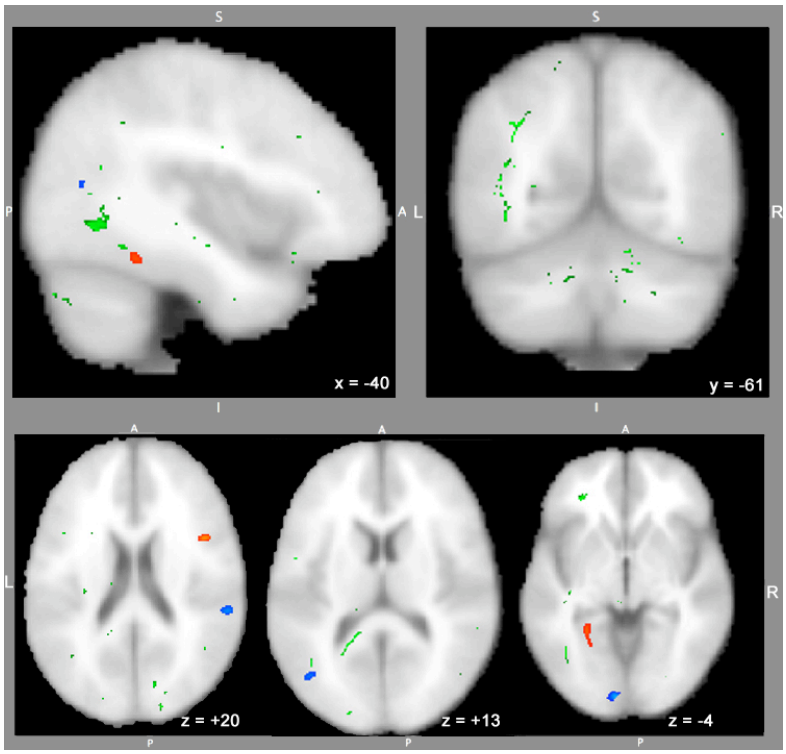

Figure 1 – Contrast synaesthetes > controls

Shown are brain areas with significantly increased grey matter volumes (GM: *red*), white matter volumes (WM: *blue*) and higher fractional anisotropy (FA: *green*) in synaesthetes. In GM and WM contrasts voxels with a t-value > 3.45 are shown; in FA contrast voxels with a p-value < 0.01 (t: 2.48, df: 26). All results are projected on a standardized brain (MNI152). X, y or z-values indicate the slice in MNI-space.

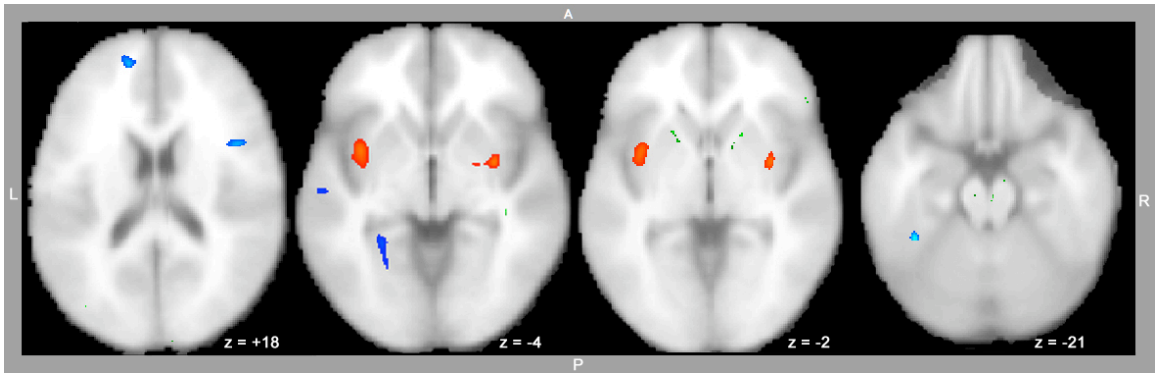

Figure 2 – Contrast controls > synaesthetes

Shown are brain areas with significantly reduced grey matter volumes (GM: *red*), white matter volumes (WM: *blue*) and lower fractional anisotropy (FA: *green*) in synaesthetes. In GM and WM contrasts voxels with a t-value < -3.45 are shown; in FA contrast voxels with a p-value < 0.01 (t: -2.48, df: 26). All results are projected on a standardized brain (MNI152).

4.8. Appendix

		MNI-coordinates			***Max./min. t-value***	***Brain region(s) in the cluster***
		X	**Y**	**Z**		
Synaesthetes > Controls						
	GM	45	10	19	4.77	Right inferior frontal gyrus
		-26	-49	-3	4.31	Left lingual gyrus
		-40	-46	-17	3.75	Left fusiform gyrus
	WM	-8	-92	-4	4.95	Left calcarine sulcus / lingual gyrus
		58	-34	20	4.66	Right insula
		-44	-70	13	3.91	Left middle temporal gyrus
	DTI	-29	40	-4	4.06	Left middle frontal gyrus
		-40	-62	-4	3.52	Left middle temporal gyrus / fusiform gyrus
		-18	-50	13	3.17	Left posterior cingulate cortex
Controls > Synaesthetes						
	GM	32	-3	-6	-4.65	Right putamen and insula
		-37	3	-5	-4.45	Left putamen and pallidum
	WM	-40	-44	-21	-5.69	Left fusiform gyrus
		46	10	19	-5.02	Right inferior frontal gyrus
		-15	53	19	-4.96	Left superior frontal gyrus
		-25	-47	-5	-3.98	Left lingual gyrus
		-57	-19	-4	-3.85	Left superior temporal gyrus
	DTI	17	12	2	-2.94	Right putamen / pallidum / caudate nucleus
		-17	11	-2	-2.69	Left putamen / pallidum / caudate nucleus

This section describes the method used in Experiments 2 and 3. The principle of Transcranial Direct Current Stimulation is explained. The concrete applications of the method are described in Section 7 and 8.

5.1. Transcranial Direct Current Stimulation (tDCS)

The Transcranial Direct Current Stimulation (tDCS) is the application of a weak direct current on the scalp (normally from 0.5 to 2mA) in order to modulate neural activity. For the induction of the direct current two electrodes are positioned on predefined positions on the scalp. Normally, positions referring to the extended 10-10-system from Electroencephalography are used. One electrode forms the positive pole (anode), the other forms the negative pole (cathode). Firing increases when the positive pole or electrode (anode) is located near the cell body or dendrites, and decrease when the field is reversed. Previous studies have shown that brain areas under the anode are activated, while areas lying under the cathode are inhibited (Bindman, Lippold, & Redfearn, 1964). It is assumed that the effect of stimulation occurs via a modulation of the resting potential of the neurons (Purpura & McMurtry, 1965). The fact that there must always be an activating and an inhibiting pole makes it difficult to create a condition of only exciting or inhibiting effect. Normally, this problem is solved by positioning one electrode on the nasion or the mastoid. Nevertheless, it is still not clear which positions should be chosen to maximize the effect of stimulation.

Figure 4: The tDCS apparatus used in Experiment 2 and 3.

It is important to note that tDCS uses a different principle than transcranial magnetic stimulation (TMS) or electrical stimulation of the brain. It does not cause, but only facilitates the firing of a cell. Therefore, tDCS does not evoke muscle twitches known from TMS.

The effect of a DC-Stimulation longer than five minutes lasts after the termination of the stimulation. Nitsche & Paulus (2001) found an after-effect of the DC-Stimulation in the range of the length of the stimulation time. Stimulations longer than nine minutes might also cause after-effects longer than forty minutes. As tDCS can lead to a slight itching on the scalp, after-effects have the great experimental advantage that subject can perform a task without any simultaneous stimulation.

TDCS has been shown to be able to change behaviour in a specific direction. One of the first reports of behavioural changes showed that contralateral anodal stimulation of the motorcortex leads to a better performance in a discrimination task (Elbert, Lutzenberger, Rockstroh, & Birbaumer, 1981).

A very promising application is the therapeutic use of tDCS. There have been beneficiary effects on patients suffering from stroke (Hummel et al., 2006), epilepsy (Fregni, Otachi et al., 2006), chronic pain (Fregni, Boggio, Lima et al., 2006) and Parkinson's disease (Fregni, Boggio, Santos et al., 2006).

PRESENCE

In this section we give a short introduction to the concept of presence – the topic of Experiments 2 and 3. In particular, we focus on presence in the context of neuroscience. We will also discuss the important question of how to measure presence.

6.1. Presence in Neuroscience

Presence is a widely used concept that appears in different contexts. It can be found in religious or spiritual practices (e.g. meditation) and has also been the object of neuroscientific research. In meditation research, a *present state* has been defined as *"an art of efficient management of attentional energy with total engagement"* (Deshmukh, 2006). A slightly different approach to *presence* is used in this thesis. Here we define *presence* as *"the feeling of being there"* (Sanchez-Vives & Slater, 2005). More generally, *presence* means the awareness of one's current spatio-temporal location. New approaches using virtual environments have been made possible by advanced computer techniques. In such experiments, a different location can be simulated with virtual scenes. A subject entering such a scene might experience a subjective dislocation into the virtual environment (VE). This subjective state of being present in a *"location different from the location in the physical world"* (Schubert, Friedmann, & Regenbrecht, 2001) has become the new standard approach for the investigation of *presence* in neuroscience (Slater, Steed, McCarthy, & Maringelli, 1998). In some experiments, the concept of *presence* in a VE has been specified with the expression *spatial presence* paraphrasing the illusion of dislocation in a virtual space (Baumgartner, Valko, Esslen, & Jancke, 2006).

6.2. Measuring Presence

6.2.1. Questionnaires

One crucial question in the context of presence research is how to measure the subjective feeling of presence in a VE. The traditional way is asking the subjects about their subjective feeling in a questionnaire (Baumgartner et al., 2006). Different specific presence questionnaires have been developed in order to allow standardized testing

(Vorderer et al., 2004; Witmer & Singer, 1998). However, there is an ongoing controversy about the different concepts used, and about the possibilities afforded by of the existing questionnaires (Slater, 1999). Moreover, questionnaires have to inherent problems. First, questionnaires are normally completed outside the VE and are therefore not simultaneous measures of presence; and secondly, they require a degree of intellectual capacity. The subject must be capable of introspection, which is especially challenging for children. In order to overcome these difficulties, alternative attempts to measure psychophysiological parameters have been developed.

6.2.2. Psychophysiological Measures

One crucial criterion of presence is to *"act as if the VE were real"* (Slater et al., 1998). If a subjects has entered the VE and forgets about being in a VE it will react and act as in the real world. It has been shown that the possibility of actions in a VE can enhance the feeling of presence (Slater et al., 1998). Besides reactions on a behavioural level, there are experiments measuring autonomic body responses as hart rate, electro-dermal activity or respiration rate. The advantages of the latter are the simultaneous data registration and the automaticity of the response. There have been different experiments using psychophysiological measures in the context of presence research and VE (Baumgartner et al., 2006; Slater, Guger et al., 2006).

6.3. Therapeutic application of presence in VE

There have been attempts to use immersive virtual environments for the treatment of mental disorders (North, North, & Coble, 1998). For example, there is an investigation with subjects suffering from social phobia. The exposure in a virtual public speech paradigm led to similar autonomic responses as in a real public speech situation (Slater, Pertaub, Barker, & Clark, 2006). Post-traumatic stress and fear of flying exposure in a VE has also shown therapeutic effects (Rothbaum et al., 2006; Rothbaum, Hodges, Ready, Graap, & Alarcon, 2001). The use of VE as a well-controlled situation for gradual exposure might be an interesting method for future psychotherapy.

EXPERIMENT 2

Brain stimulation modulates driving behavior

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7.1. Abstract

Driving a car is a difficult multitask requiring coordinated functioning of distributed brain regions. Controlled and safe driving depends on the integrity of the dorsolateral prefrontal cortex (dlPFC), a brain region, which has been shown to mature in late adolescence. Our experiments show that external modulation of the dlPFC using transcranial direct current stimulation (tDCS) directly influences driving behavior in a high-end driving simulator. Excitation of the dlPFC (by applying anodal tDCS) leads to a more careful driving style in virtual scenarios without the participants noticing changes in their behavior. Remarkably, this study is one of the first to prove that external stimulation of a specific brain area can influence a multi-part behavior in a very complex and everyday-life situation, therefore breaking new ground for therapy at a neural level.

7.2. Introduction

Standardized so-called "gambling tasks" in which participants can win or loose money by drawing cards from different decks have become an established tool for the investigation of "risk behavior" in psychological and neurophysiological research (Iowa Gambling Task: Bechara, Tranel, & Damasio, 2000; Manes et al., 2002; Cambridge Gambling Task: Rogers et al., 1999). Typically, riskier behavior in these tasks leads to higher gains but also to higher losses. The standardization of such tasks is crucial in the context of, for example, the diagnosis of patients with problems with impulsivity or in planning and decision-making.

At a neural level, decision-making, risk-taking behavior and impulsiveness share similar neural networks in the lateral dorsal prefrontal cortex (ldPFC) (Bechara et al., 2000). Patients with lesions in the ldPFC (especially in the right dlPFC) show riskier behavior (Clark, Manes, Antoun, Sahakian, & Robbins, 2003), while lesions in the ventro-medial PFC lead to "myopia" for the future, that is, an insensitivity for future consequences of present behavior (Bechara et al., 2000). Interestingly, recent studies showed that external stimulation of the dlPFC with Transcranial Magnetic Stimulation (Knoch et al., 2006) and with Transcranial Direct Current Stimulation (Fecteau et al., 2007) can influence risk-taking behavior.

The dlPFC is a brain region that matures through to late adolescence (Gogtay et al., 2004), and even during the second decade of life (Klingberg, Vaidya, Gabrieli, Moseley, & Hedehus, 1999). The late myelination of the dlPFC can partly explain why adolescents' behavior is characterized by motivational difficulties, addiction and impulsivity (Chambers, Taylor, & Potenza, 2003). The fact that driving accidents are the main cause of death for adolescents and young adults is a problem of paramount importance, also from a political perspective (Patil, Shope, Raghunathan, & Bingham, 2006).

Different studies have shown that risky driving behavior is more prominent among young drivers (Bina, Graziano, & Bonino, 2006). The frequency of substance abuse and the degree of aggressiveness are (besides gender and social factors) the main predictors for risky driving (Fergusson, Swain-Campbell, & Horwood, 2003). Furthermore, children diagnosed with ADHD have an elevated risk for driving-related problems in adulthood (Thompson, Molina, Pelham, & Gnagy, 2007). In view of the preceding, we may assume that the dlPFC is an important neural structure in modulating risky driving behavior. Results from the standardized "Risk-" and "Gambling-Tasks" are consistent with the findings about the neurodevelopment of the dlPFC, but the generalization of findings to everyday life situations is hampered by the high specificity of these paradigms.

The aim of this study was to examine the role of the dlPFC in a situation more closely associated with risk taking in everyday life. We hypothesized that excitation of the dlPFC leads to more executive control and less risky driving behavior. In order to test this hypothesis, we modulated the participants' PFC while they were driving in a driving simulator.

In contrast to an earlier study on external brain-modulation and risk behavior (Knoch et al., 2006), we used tDCS (transcranial Direct Current Stimulation) instead of TMS (Transcranial Magnetic Stimulation). tDCS has the combined advantages that the participants barely notice the stimulation, the modulation is easy to alter between an activating and an inhibiting condition, and that it allows for a reliable sham condition.

7.3. Methods

7.3.1. Subjects

Twenty-four male subjects participated in the study. Twenty-one of them were students. All participants were between 20 and 30 years old (mean age: 24.1; SD: 2.7). Male subjects were chosen because in pilot experiments men were found to have a lower probability of experiencing nausea in the driving simulator. All of the participants were right-handed, had no history of neurological or psychiatric diseases and were in the possession of a driver's license for at least 2 years.

7.3.2. Design

Every subject was tested on two different days within a week. On the first day, after a theoretical instruction about the driving simulator and the transcranial Direct Current (tDCS) stimulation, all subjects gave their written consent for participation in the experiment and filled in a questionnaire about their driving behavior (frequency of driving and years in possession of driver's license) education and health. Before the actual experiment, participants had the opportunity to drive a sample course ("circuit") in the driving simulator in order to get used to the simulation.

For the actual experiment, the course called "Mountain Course" (www.drfoerst.de) was chosen (see below for details). Every participant drove the same course twice. Between the two courses a tDCS stimulation (see below for details) was applied on the dlPFC for 15min. Half of the subjects were stimulated on the right hemisphere, the other half on the left. Because of reports of long-lasting after-effects (until 90min) (Nitsche & Paulus, 2001) the "baseline-drive" (without an influence of the tDCS) always preceded the stimulation. During the stimulation with tDCS, the participants sat outside the driving simulator on a chair. In order to distract subjects from the stimulation they filled in questionnaires about handedness (Annett, 1970). To assess subjective involvement in the virtual environment, an adapted version of the MEC-SQ (Spatial-presence-questionnaire) was filled in by the participants (Vorderer et al., 2004) after every trial. The possible impact of the DC-stimulation on emotional state was assessed using the Self-Assessment-Manikin (Bradley & Lang, 1994) before and after stimulation. On the second day, exactly

the same procedure was applied with however a changeover of the active and reference electrodes for modulation (i.e. cathodal for anodal and anodal for cathodal stimulation). The questionnaires about health and handedness were not filled in on this second day.

7.3.3. Driving Simulator

The Driving Simulator used in the experiment is an upgraded version of the F10PF-Model of the Dr.-Ing. Reiner Foerst GmbH (www.drfoerst.de). The virtual environment was projected on three 61in Videowalls (RP 61" ES LCD; www.hantarex.it).

The actual test-course, called "Mountain Course", consists of a car that can be driven on a road starting outside a small village, passing through a village with traffic lights, and then following a route through built up areas. The simulation automatically stopped after a covered distance of 3km (around 3.5min depending on driving speed). The scene was identical for every subject. Traffic, traffic lights, dangerous events (children, animals) etc. are simulated randomly in order to enhance the reality of the scene. Every 20 ms, about 30 measures with which to capture driving behavior were registered (e.g. driving speed, distance to driver ahead, position in the course, position of break, accelerator, gear, revolutions per minute, lateral distance from road mid-line etc.).

7.3.4. Direct Current Stimulation

The "DC-Stimulator" by Eldith© (www.eldith.de) was used for transcranial Direct Current Stimulation (tDCS). The constant current was applied through two saline-soaked electrodes with a surface of 35mm^2. Based on earlier studies modulating the dlPFC (Knoch et al., 2006), stimulation occurred at F3- resp. F4-position (international EEG 10-20-system). The anode electrode was positioned on F3 resp. F4 for the excitation of the dlPFC and on the ipsilateral mastoid for the cathode electrode. For inhibition, the two electrodes were switched (cathode over F3/F4, anode over ipsilateral mastoid). Subjects (n=24) were divided randomly into two equal groups. One group was stimulated on the left, the other on the right hemisphere.

The stimulation lasted 15min at a constant current intensity of 1mA. The system automatically turns off the stimulation when the electrical resistance is too high.

7.4. Results

Figure 1 shows the results of the within subject variable (kind of modulation). Depicted are differences in driving behavior before and after DC-stimulation (POST minus PRE). Significant differences between anodal and cathodal modulation were found in *Driving Speed* ($p<.02$), *Distance to driver ahead* ($p<.03$), *Number of speed violations in built-up areas* ($p<.01$) and *Resolutions per minute* ($p<.03$). When PFC-activity was enhanced, *Driving Speed*, *Speed violations* and *Revolutions per minute* were reduced, while the *Distance to driver ahead* was enhanced. All four variables indicate a more cautious driving behavior during activated PFC.

Inhibition of the PFC led to a slightly but not significantly enhanced risky behavior. Comparison of PRE-POST measurements in the two conditions suggests that learning effects cannot explain the differences found. But, over all, participants did show a tendency to drive more carefully after DC-stimulation.

Figure 2 shows the results of the between subject variable (hemisphere of stimulation). The four variables are shown for the two groups separately. There are no significant interactions between side of stimulation (hemisphere) and kind of stimulation (Excitation vs. Inhibition). However, the tendency was stronger for effects of DC-stimulation on the right hemisphere.

Subjects did not indicate different degrees of presence in the virtual scene in the different conditions, and there were no differences in emotion either, as reported with the Self-Assessment Manikin. None of the subjects reported nausea during driving simulation. The years in possession of a driver's license were not associated with different effects of DC-stimulation.

7.5. Discussion

External activation of the PFC leads to less risky driving behavior compared with the inhibition of PFC. The behavioral differences were found in four variables (*Driving speed, Distance to driver ahead, Number of speed violations, Revolutions per minute)* measuring very different aspects of driving behavior. This result is even more surprising because the participants were not aware of their changes in behavior. The fact that

inhibition did not lead to significant changes in behavior can partly be explained by the electrical stimulation. Even if the stimulation only evoked a slight itching, the application of electrical current might have caused the participants to drive slightly more carefully. This tendency is in line with Fecteau et al. (2007) who found the same effect of DC-Stimulation. The effect of inhibition of PFC (compared with baseline) might have been diminished by this tendency. Nevertheless, the comparison of the two modulating conditions is independent of this stimulation effect.

The crucial involvement of the PFC for risky driving behavior found in this study is in line with previous findings about the PFC (Bechara et al., 2000). It is remarkable that PFC-activation is directly correlated with such a complex behavior as driving a car, and it is even more astonishing that this complex behavior can be influenced by external modulation of the brain. The tendency of stronger effects of DC-stimulation on risk-taking behavior on the right hemisphere are consistent with findings by Clark et al. (2003) reporting the same lateralization effect in patients with brain lesions in the context of risk behavior.

It is important to highlight the significance of the present findings for the explanation of aggressive and risky driving behavior, especially in adolescents. Regardless of the high behavioral complexity in this paradigm, we found striking results with high external validity and direct transferability in everyday life. Moreover, the feasibility of external manipulation of the brain, even on complex behaviors, opens different possibilities for neural therapy.

7.6. Acknowledgements

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7.7. Literature

Annett, M. (1970). A classification of hand preference by association analysis. *Br J Psychol., 61*(3), 303-321.

Bechara, A., Tranel, D., & Damasio, H. (2000). Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. *Brain, 123*(11), 2189-2202.

Bina, M., Graziano, F., & Bonino, S. (2006). Risky driving and lifestyles in adolescence. *Accident Analysis & Prevention, 38*(3), 472-481.

Bradley, M. M., & Lang, P. J. (1994). Measuring emotions: The Self-Assessment Manikin and the Semantic Differential. *Journal of Behavior Therapy and Experimental Psychiatry, 25*, 49-59.

Chambers, A. R., Taylor, J. R., & Potenza, M. N. (2003). Developmental Neurocircuitry of Motivation in Adolescence: A Critical Period of Addiction Vulnerability. *Am J Psychiatry, 160*, 1041-1052.

Clark, L., Manes, F., Antoun, N., Sahakian, B. J., & Robbins, T. W. (2003). The contributions of lesion laterality and lesion volume to decision-making impairment following frontal lobe damage. *Neuropsychologia, 41*(11), 1474-1483.

Fecteau, S., Pascual-Leone, A., Zald, D. H., Liguori, P., Theoret, H., Boggio, P. S., et al. (2007). Activation of Prefrontal Cortex by Transcranial Direct Current Stimulation Reduces Appetite for Risk during Ambiguous Decision Making. *J. Neurosci., 27*(23), 6212-6218.

Fergusson, D., Swain-Campbell, N., & Horwood, J. (2003). Risky driving behaviour in young people: prevalence, personal characteristics and traffic accidents. *Aust N Z J Public Health, 27*(3), 337-342.

Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, C. A., et al. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *PNAS, 101*(21), 8174-8179.

Klingberg, T., Vaidya, C. J., Gabrieli, J. D. E., Moseley, M. E., & Hedehus, M. (1999). Myelination and organization of the frontal white matter in children: a diffusion tensor MRI study. *NeuroReport, 10*, 2817-2821.

Knoch, D., Gianotti, L. R. R., Pascual-Leone, A., Treyer, V., Regard, M., Hohmann, M., et al. (2006). Disruption of Right Prefrontal Cortex by Low-Frequency Repetitive Transcranial Magnetic Stimulation Induces Risk-Taking Behavior. *J. Neurosci., 26*(24), 6469-6472.

Manes, F., Sahakian, B., Clark, L., Rogers, R., Antoun, N., Aitken, M., et al. (2002). Decision-making processes following damage to the prefrontal cortex. *Brain, 125*(3), 624-639.

Nitsche, M. A., & Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology, 57*(10), 1899-1901.

Patil, S. M., Shope, J. T., Raghunathan, T. E., & Bingham, C. R. (2006). The Role of Personality Characteristics in Young Adult Driving. *Traffic Injury Prevention, 7*(4), 328 - 334.

Rogers, R. D., Everitt, B. J., Baldacchino, A., Blackshaw, A. J., Swainson, R., Wynne, K., et al. (1999). Dissociable Deficits in the Decision-Making Cognition of

Chronic Amphetamine Abusers, Opiate Abusers, Patients with Focal Damage to Prefrontal Cortex, and Tryptophan-Depleted Normal Volunteers: Evidence for Monoaminergic Mechanisms. *Neuropsychopharmacology, 20*, 322-339.

Thompson, A. L., Molina, B. S. G., Pelham, W., Jr., & Gnagy, E. M. (2007). Risky Driving in Adolescents and Young Adults with Childhood ADHD. *J. Pediatr. Psychol.*, jsm002.

Vorderer, P., Wirth, W., Gouveia, F. R., Biocca, F., Saari, T., Jäncke, F., et al. (2004). MEC Spatial Presence Questionnaire (MEC-SPQ): Short documentation and Instructions for Application. Report to the European Community, Project Presence: MEC (IST-2001-37661).

7.8. Figures

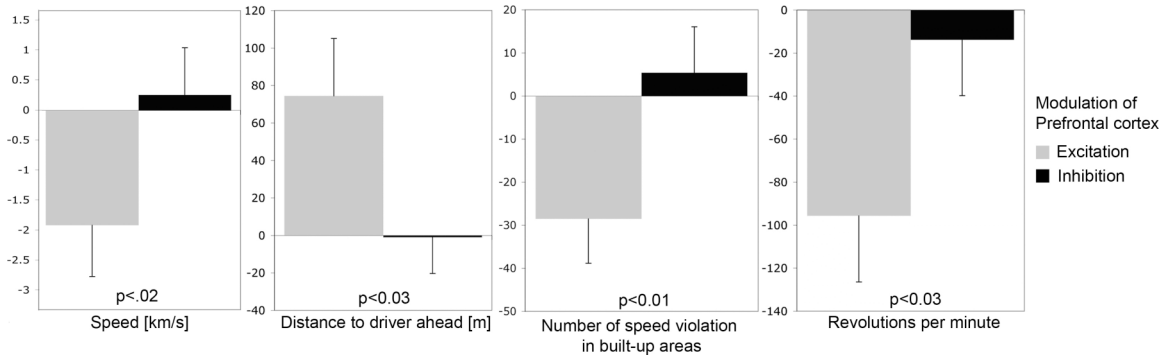

Figure 1:

Within subject variable (kind of modulation). Depicted are differences (±Standard Error) in driving behavior before and after DC-stimulation (POST minus PRE). The p-values indicate the significance of the differences of the two kinds of modulation (Inhibition vs. Excitation) of the Prefrontal Cortex.

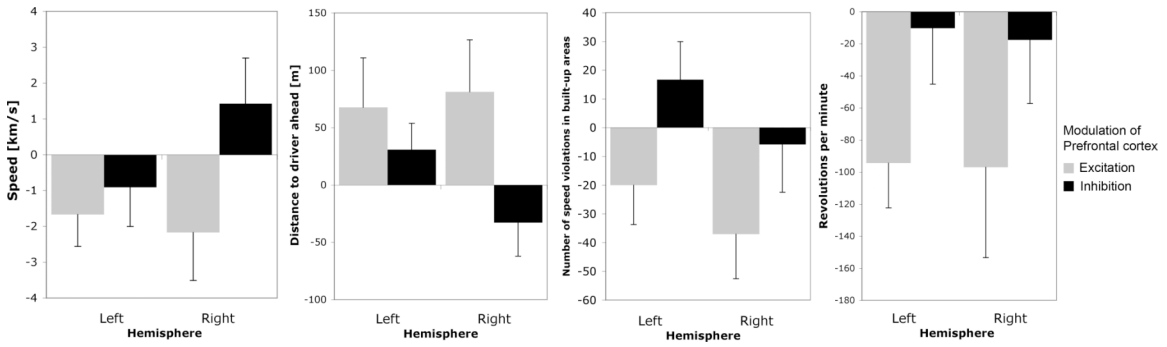

Figure 2:

Between subject variable (side of stimulation). Depicted are differences (±Standard Error) in driving behavior before and after DC-stimulation (POST minus PRE) for each group (hemisphere of stimulation) separately. The interaction between side of stimulation and kind of stimulation is not significant in any variable. However, there are tendencies of interactions in the variables Speed (p<.12) and Distance to driver ahead (p<.27) indicating stronger effects of external modulation on the right hemisphere.

EXPERIMENT 3

Modulating presence and impulsiveness by external stimulation of the brain

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8.1. Abstract

8.1.1. Background

"The feeling of being there" is one possible way to describe the phenomenon of feeling present in a virtual environment and to act as if it were real. One neural basis of this phenomenon is located in the dorso-lateral prefrontal cortex, an area also associated with executive control.

8.1.2. Methods

In our experiment we stimulated the right dorso-lateral prefrontal cortex with transcranial Direct Current (tDC) in order to modulate this experience of presence while watching a virtual rollercoaster ride. During the ride we registered the electro-dermal activity. Subjects also performed a test for impulsiveness and answered a questionnaire about their presence in the virtual environment.

8.1.3. Results

Our results show that the stimulation led to a more impulsive behavior and a higher EDA response if the right frontal cortex was inhibited.

8.1.4. Conclusions

Besides typical functions of the right dlPFC, tDC-stimulation could also modulate the EDA response in a virtual scenario by external stimulation of the brain. Moreover, our results show that changes of the body response in the virtual environment can occur without changes of the conscious subjective experience.

The effects can be explained by executive control theories of the PFC brain region and suggest a possible use of therapeutic external brain stimulation in the context of addiction and impulsiveness.

8.2. Background

When we are watching a movie, reading a book or playing a computer game we sometimes experience the virtual reality as if it were real. This subjective sensation of presence is referred as "the feeling of being there". From an earlier EEG (electroencephalography) study [1] and our own fMRI (functional magnetic resonance imaging) data, we know that activations in certain brain areas (especially in the prefrontal cortex) are negatively correlated with the subjective feeling of presence in another space (spatial presence). The involvement in a virtual scene can be measured by questionnaires (e.g. MEC-SPQ [2]). Moreover, also psychophysiological measures (e.g. electro-dermal activity, EDA) can indicate the degree of presence in a virtual environment (VE) of a person. A higher involvement was found to correlate with an enhanced EDA response [1].

New methods as the transcranial Direct Current Stimulation (tDCS) allow modulating brain activity by applying a Direct Current to the brain [3]. Obviously, the interesting question arises, if the feeling of presence can be influenced by an external stimulation of the responsible brain areas.

The dorso-lateral prefrontal cortex (dlPFC) is known to be an important neural correlate of controlling behavior, normally referred to as “executive functions” [4]. Its main function is the inhibition of impulsive behavior initiated by other brain-regions (e.g. the brainstem, basal ganglia). Its role in eliciting presence can therefore be explained by a lowered control and less cognitive evaluation of the virtual scene. The frontal cortex matures until late adolescence [5]. The late myelination of the dlPFC can partly explain why adolescents’ behavior is characterized by motivational difficulties, impulsivity and addiction (also in the context of videogames and virtual scenes) [6].

In our study we stimulated – based on local maxima of activation found in our fMRI pilot experiments – the right dlPFC with Direct Current while participants were watching a virtual rollercoaster scene.

In order to evaluate the success of the stimulation, we also conducted the classical Go-Nogo task. The performance in this test depends on the functioning of dlPFC [7] and indicates the degree of impulsivity. There is evidence, that the task performance in the

Go-Nogo task can be influenced by DC-stimulation of the left dlPFC [8] and with other methods also on the right dlPFC (transcranial magnetic stimulation (TMS); [9]).

We hypothesized that the feeling of being present in the virtual environment is enhanced if the dlPFC is inhibited and that participants show higher impulsiveness. On the other hand, an excitation of the dlPFC should lead to a lowered presence experience and reduced impulsiveness.

8.3. Methods

8.3.1. Subjects

Thirty-five (17 female, 18 male) subjects participated in the experiment. Most of them being students of the University of Zurich. The mean age was 24.9 (±3.7). All of the participants were right-handed, had no history of neurological or psychiatric diseases and gave their informed consent for the participation in the experiment.

8.3.2. TDC-Stimulation

In order to prevent an interaction between the two brain-hemispheres we decided to constrain the transcranial Direct Current Stimulation (tDCS) to one hemisphere. In pilot experiments in our lab we found slightly stronger correlations between presence-experience and brain activation on the right dorso-lateral prefrontal cortex (rdlPFC) than on the left side. Therefore, we only stimulated the right prefrontal cortex. The stimulation side was set on directly above the local maxima of activation (FC3 in the international EEG 10-20-System). In order to constrain brain stimulation to one hemisphere the reference electrode was placed on the ipsilateral mastoid.

For stimulation the "DC-Stimulator" by Eldith© (www.eldith.de) was used. The constant current was applied through two saline-soaked electrodes with a surface of 35mm2. For the excitation of the dlPFC the anode electrode was positioned on FC3 and the cathode electrode on the ipsilateral mastoid. For the inhibition, the two electrodes were switched (cathode over FC3, anode over ipsilateral mastoid). The stimulation lasted 5.5 min at a constant current intensity of 1.5mA. The system automatically turned off the

stimulation when the electrical resistance was too high. For sham stimulation the stimulator was switched off.

8.3.3. Rollercoaster

The subjects were sitting on a chair while watching three different rollercoaster scenarios on a 22-inch computer screen placed at a distance of 60 cm in front of them. The rollercoaster scenarios were taken from a commercially available rollercoaster simulation software (www.nolimitscoaster.com). Realistic driving noises were presented on loudspeakers. Every scenario consisted of three different phases. It started with an "ascending phase" (30 sec) followed by a "dynamic phase" with movements in different dimensions and very high speed (60 sec) and an "end-phase" with low speed and without inclination (Figure 1).

8.3.4. Psychophysiological Measures

During the rollercoaster ride electro-dermal activity (EDA) and an electro-myogram (EMG) were registered. The EDA and EMG measurements were made using a commercially available device (PAR-PORT; Hogrefe Company, Germany). For EDA recording, electrodes were attached to the thenar and hypothenar areas on the palm of the left hand. Beside the EDA-level another quantification of EDA was obtained by the summation of the EDA amplitude called EDA sum-amplitude. In addition, log-transformation (log[EDAsumamp+1]) was used to normalize the EDA amplitude data. The EMG electrodes were attached at the left Musculus corrugator supercilii.

8.3.5. Go-Nogo Task

In order to measure on one hand the influence of rdlPFC stimulation and on the other hand the interconnection between impulsivity and the involvement in a virtual environment, subjects performed a Go-Nogo Task, a standard test for impulsivity (Testbatterie zur Aufmerksamkeitsprüfung, TAP, [10]). Out of 5 types of stimuli with lines in different directions the subject has to press a button if one of the two defined target stimuli is presented. 100 stimuli are presented, 40 of them are target stimuli. The

rate of False Alarms (FA, button-press when seeing a non-target stimulus) indicates the degree of impulsivity.

8.3.6. Questionnaires

Besides autonomic body responses, the degree of presence in the virtual environment can be measured with questionnaires. We used an adapted version of the spatial presence questionnaire MEC-SPQ [5]. The questionnaire was presented to the subjects right after the rollercoaster ride. Participants could indicate their degree of presence on a visual analog scale. Moreover, the SAM (Self Assessment Manikin) was answered after every ride in order to control for mood changes by the DC-stimulation. The two question about arousal and valence of the presented stimuli were applied.

We were also interested in the influence of Sensation Seeking personality on presence experience and therefore asked the subject to answer to the TAS (Thrill and Adventure Seeking Scale) a subscale of the Sensation Seeking Scale.

Furthermore, we presented a standard handedness questionnaire to the subjects.

8.3.7. Design

Every subject repeated three times the trial shown in Figure 2. Three different kinds of stimulation (anodal, cathodal, sham) were randomly assigned to the trials. All subjects therefore received every kind of stimulation in random order.

8.4. Results

8.4.1. Go-Nogo Task

Figure 3 shows the results of the Go-Nogo Task. During cathodal stimulation of the dlPFC, participants more often pressed the button when seeing non-target stimuli (false alarms), which indicates a higher frequency of impulsive behavior. There was no performance improvement during anodal stimulation. The number of false alarms was significantly different in a one-way ANOVA ($F_{(2,68)} = 3.653$; $p = 0.03$). The two contrast „sham“ vs. „cathodal“ ($p = 0.032$) and „anodal“- vs. „cathodal“ ($p = 0.033$) were both significant.

8.4.2. Psychophysiological Measures

Only data of 29 participants could be used for analysis of psychophysiological measures. The EMG measure during the rollercoaster ride showed no significant difference, in electro-dermal activity (EDA) however, different aspects varied as hypothesized.

Figure 4 shows a clear SCR with the start of the virtual rollercoaster ride. In the first 30 seconds of the rollercoaster ride (ascending phase), subjects showed higher EDA-levels under cathodal stimulation ($F_{(2,56)} = 3.237$; $p = 0.047$; cathodal > sham: $p = 0.021$). The one-way ANOVA of the EDA-sum-amplitudes was not significant ($F_{(2,56)} = 3.016$; $p = 0.057$), only the contrast cathodal > anodal reached significance level ($p = 0.037$).

Figure 5 shows the peak skin conductance level (SCL) within the first 12 seconds of the rollercoaster ride. Maximal SCL were significantly different in the three conditions ($F_{(2,56)} = 4.958$ $p = 0.01$) with a higher peak during cathodal stimulation vs. anodal stimulation ($p = 0.005$) and vs. sham stimulation ($p = 0.012$).

8.4.3. Presence- and Personality Questionnaires

The subjective reports in the adapted version of Self-location scale out of the MEC-SPQ showed no significant differences between the conditions. Interestingly, there was no significant correlation between the subscale “Thrill and adventure seeking” (TAS) and the EDA response differences ($p>.33$).

The Self-Assessment-Manikin (SAM) showed no differences in the felt valence of the stimuli ($F_{(2,66)} = 1.617$; $p = 0.206$), or the evoked arousal ($F_{(2,66)} = 2.532$; $p = 0.087$). Electrical current (anodal and cathodal condition) tend to enhance the general arousal compared to sham stimulation.

8.4.4. Correlation between Go-Nogo Task and EDA

The differences in the test of impulsiveness and the EDA reaction show highly significant correlation ($r = 0.42$, $p < 0.02$). If participants act more impulsively in the Go-Nogo Task, they show stronger SCR impulses in the ascending phase of the rollercoaster ride.

8.5. Discussion

The results of the Go-Nogo Task show that we could modulate the degree of a subject's impulsiveness by stimulating the right dlPFC with tDCS. The modulation showed significant differences in behavior when the dlPFC was inhibited leading to a more impulsive behavior. The excitation of the dlPFC did not lead to a less impulsive behavior, probably because the task was too easy and therefore already "normal" activation of dlPFC was sufficient to solve the task. This fact might also explain different findings in previous studies using a more difficult and a slightly different version of the Go-Nogo task [8, 9].

The results from psychophysiological measures show that participants had higher autonomic body responses (EDA) when watching the virtual rollercoaster if their dlPFC was inhibited. The differences in skin conductance occurred in the first phase of the rollercoaster ride. This phase consisted of an ascending ride with steep inclination. The strong response in EDA while ascending might be caused by the expectation of the dynamic phase and the knowledge of autonomic body responses in a real rollercoaster.

The correlation between the Go-Nogo Task and the EDA response shows that both, the impulsive behavior and the autonomic responses in EDA can be influenced by the DC-stimulation and that both reactions might depend on activations in similar brain regions. However, further tests are needed for a better understanding of the interlinkage between impulsiveness and EDA-responses.

The fact that the personality trait of TAS (Thrill and adventure seeking) could not predict a change in behavior or EDA response shows that brain stimulation of rdlPFC can be applied independent of Sensation Seeking personality. Nevertheless, there might still be different effects on patients as found in patients with major depression [9].

A very important result of the present study is the fact that there were significant differences in EDA measures in the hypothesized direction, but not in the subjective reports in the questionnaires. This shows on one hand that subjective measures might not be reliable in the context of presence-research (especially because the involvement in a VE requires low cognitive control), on the other hand, it shows that brain stimulation can lead to a change in bodily reactions without changes in subjective reports.

8.6. Conclusions

A stimulation of the right dlPFC with Direct Current can influence the presence experience while watching a virtual scene and the impulsiveness in a Go-Nogo task. The effects occur on an implicit level as the stimulations did not influence the reports in specific presence questionnaires. Moreover, there were only effects during the cathodal (inhibiting) condition leading to enhanced impulsiveness and higher EDA responses, but not in the anodal (exciting) condition.

8.7. Competing interests

The authors declare that they have no competing interests.

8.8. Authors' contributions

GB participated in the design of the study, performed the statistical analysis and drafted the manuscript. GC participated in the design, carried out the experiments and performed the statistical analysis. TB participated in the design. LJ participated in the design, the statistical analysis and helped drafting the manuscript. All authors read and approved the final manuscript.

8.9. Acknowledgements

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8.10. References

1. Baumgartner T, Valko L, Esslen M, Jancke L: **Neural Correlate of Spatial Presence in an Arousing and Noninteractive Virtual Reality: An EEG and Psychophysiology Study.** *CyberPsychology & Behavior* 2006, **9:**30-45.

2. Vorderer P, Wirth W, Gouveia FR, Biocca F, Saari T, Jäncke F, Böcking S, Schramm H, Gysberg A, Hartmann T, et al: **MEC Spatial Presence Questionnaire (MEC-SPQ): Short documentation and Instructions for Application. Report to the European Community, Project Presence: MEC (IST-2001-37661).** 2004.

3. Nitsche MA, Antal A, Liebetanz D, Lang N, Tergau F, Paulus W: **Induction and Modulation of Neuroplasticity by Transcranial Direct Current Stimulation.** In *Transcranial Brain Stimulation for Treatment of Psychiatric Disorders. Volume* 23. Edited by Marcolin MA, Padberg F. Basel: Karger; 2007: 172-186: *Adv Biol Psychiatr.*].

4. Wood JN, Grafman J: **Human Prefrontal Cortex: Processing and Representational Perspectives.** *Nature Reviews Neuroscience* 2003, **4:**139-147.

5. Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis CA, Nugent TF, Herman DH, Clasen LS, Toga AW, et al: **Dynamic mapping of human cortical development during childhood through early adulthood.** *PNAS* 2004, **101:**8174-8179.

6. Chambers AR, Taylor JR, Potenza MN: **Developmental Neurocircuitry of Motivation in Adolescence: A Critical Period of Addiction Vulnerability.** *Am J Psychiatry* 2003, **160:**1041-1052.

7. Menon V, Adleman NE, White CD, Glover GH, Reiss AL: **Error-related brain activation during a Go/NoGo response inhibition task.** *Human Brain Mapping* 2001, **12:**131-143.

8. Boggio PS, Bermpohl F, Vergara AO, Muniz ALCR, Nahas FH, Leme PB, Rigonatti SP, Fregni F: **Go-no-go task performance improvement after anodal transcranial DC stimulation of the left dorsolateral prefrontal cortex in major depression.** *Journal of Affective Disorders* 2007, **101:**91-98.

9. Bermpohl F, Fregni F, Boggio PS, Thut G, Northoff G, Otachi PTM, Rigonatti SP, Marcolin MA, Pascual-Leone A: **Effect of low-frequency transcranial magnetic stimulation on an affective go/no-go task in patients with major depression: Role of stimulation site and depression severity.** *Psychiatry Research* 2006, **141:**1-13.

10. Zimmermann P, Fimm B: **A test battery for attentional performance.** In *Applied Neuropsychology of Attention Theory, Diagnosis and Rehabilitation.* Edited by Leclercq M, Zimmermann P; 2002: 110-151

8.11. Figures

Figure 1 - Example of a Rollercoaster Scenario

Ascending phase (left, 30 sec), Dynamic phase (middle, 60 sec), End phase (right, 12 sec). The scenes are normally presented in color.

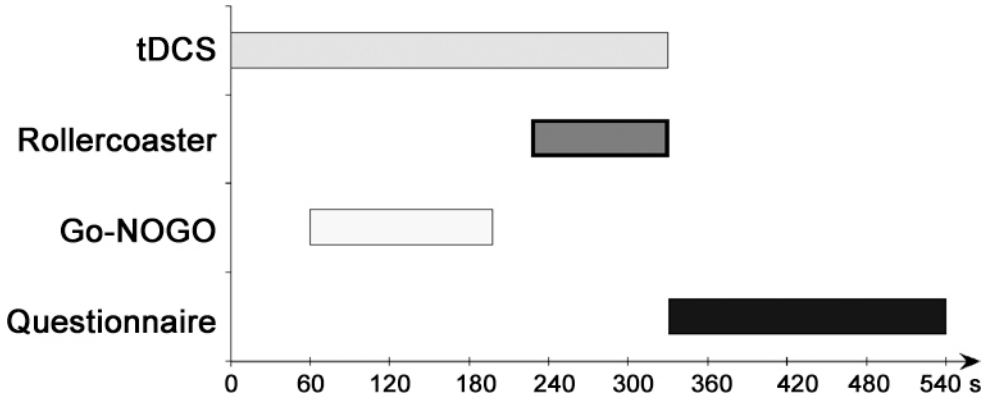

Figure 2 - Design

Sequence of different tasks and tDCS stimulation in seconds. This sequence was repeated three times per subject for the three stimulating conditions (sham, anodal, cathodal).

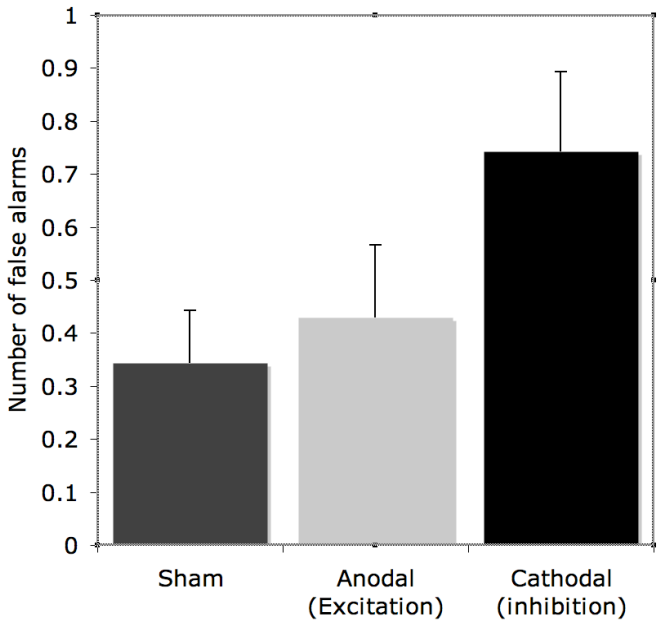

Figure 3 – Number of false alarms (FA) in the different conditions in the Go-Nogo Task.

Inhibition of the right dlPFC led to an enhanced number of FA ($p<.03$) compared to Sham and Anodal-Stimulation. Depicted are means of FA (±SE).

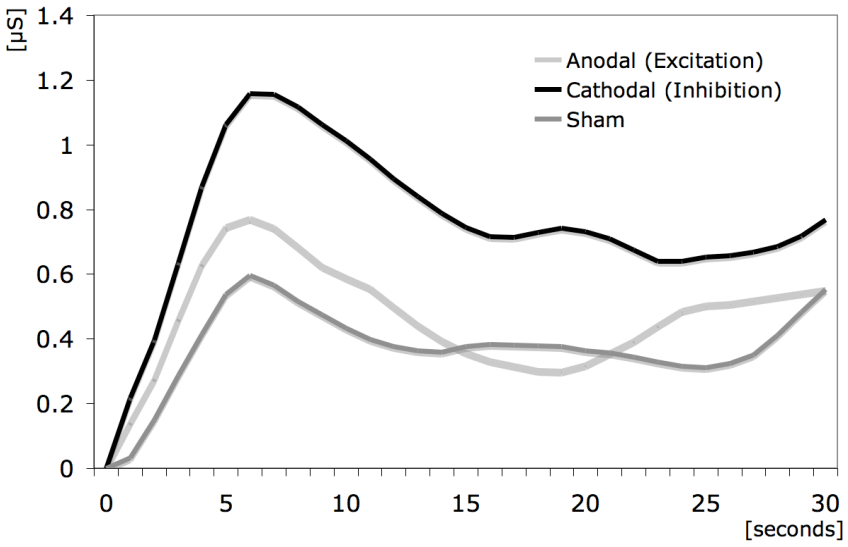

Figure 4 - Skin conductance level of the first 30 seconds of the rollercoaster ride.

Cathodal stimulation (inhibition) of the rdlPFC led to an enhanced EDA response.

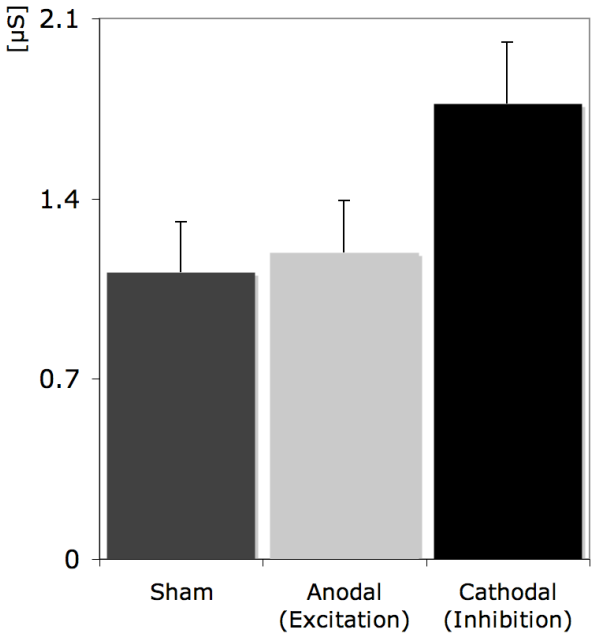

Figure 5: Peak of EDA response (maximal skin conductance level) in the first 12 seconds of the rollercoaster ride.

Cathodal stimulation (inhibition of the dlPFC) leads to significantly enhanced EDA responses ($p<.01$) during the ascending phase in the virtual rollercoaster compared to Sham and Anodal Stimulation. Depicted are means of the SCL (±SE).

GENERAL DISCUSSION

The neuroanatomical basis of colour-grapheme synaesthesia identified in **Experiment 1** is well in line with earlier functional findings about this type of synaesthesia. We found differences in the synaesthetes' brain anatomy in frontal areas, in the basal ganglia and occipito-temporal regions. As the occipito-temporal and the frontal areas can be interpreted as neural correlates of language and colour perception, they might be the basis of the specific grapheme-colour linkage. The third cluster of differences, located in fronto-basal structures, might reflect a more general neuroanatomical underpinning of synaesthesia. It would be interesting to investigate whether this difference can also be found also in other kinds of synaesthesia. We interpreted the reduced connectivity and reduced grey matter volumes in the basal ganglia as a reduced neural inhibition and a generally enhanced cortical activation through a thalamic disinhibition in synaesthetes. It suggests that such a thalamic disinhibition might also be the neural basis of the "realistic" character of synaesthetic perceptions.

In **Experiment 2** we found behavioural differences after an external modulation of the brain with Direct Current. We were able to directly influence the driving behaviour in a high-end driving simulator. An excitation of the dlPFC (by applying anodal tDCS) led to a more careful driving style in virtual scenarios without the participants noticing changes in their behaviour. This is remarkable, as our result is one of the first to prove that an external stimulation of the brain can influence a complex and multipart behaviour. On the other hand, we were not able to influence the subjective reports of presence in the virtual environment. This might have different causes. Probably, the effect was to small to have a consciously perceivable change in subjective presence. Moreover, we used a Likert-scale with seven steps, thus limiting the range of possible answers. Finnaly, we registered no psychophysiological responses.

Based on these possible reasons, we tried to modify the paradigm in **Experiment 3**. The scenario was simplified using a standardized rollercoaster ride and instead of a Likert-scale we used a visual analogue scale. Moreover, we co-registered psychophysiological measures. While subjective reports still did not significantly differ

between the different modulations of the prefrontal cortex, we could change the physiological response in electro-dermal activity (EDA). Inhibiting the right dorso-lateral prefrontal cortex led to an enhanced EDA-response and to a higher impulsivity in the Go-Nogo-Task.

The dorso-lateral prefrontal cortex is known to be involved in controlling behaviour. An inhibition of the dlPFC can lead to a riskier behaviour in a gambling task. We found that an excitation leads to more careful driving behaviour and an inhibition to more impulsive behaviour. From results in our experiments, we propose that the dlPFC – especially on the right hemisphere – is one crucial neural correlate of a person's involvement in a virtual environment. Probably, subjects control their presence in a VE via an active dlPFC by a critical analysis of the virtual scene. With less critical analysis, a subject might perceive a VE as more real and show a stronger physiological response. As there are anatomical connections between the prefrontal cortex and basal ganglia, it might be interesting to investigate whether the influence of the PFC occurs via the basal ganglia and the thalamus. If that is the case, there might be a relationship between the perception of reality in presence and synaesthesia, namely we would expect that synaesthetes to show a stronger involvement in a virtual environment.

REFERENCES

Asher, J., Aitken, M., Farooqi, N., Kurmani, S., & Baron-Cohen, S. (2006). Diagnosing and phenotyping visual synaesthesia: a preliminary evaluation of the revised test of genuineness (TOG-R). *Cortex, 42*(2), 137-146.

Baron-Cohen, S., Burt, L., Smith-Laittan, F., Harrison, J., & Bolton, P. (1996). Synaesthesia: prevalence and familiality. *Perception, 25*(9), 1073-1079.

Baumgartner, T., Valko, L., Esslen, M., & Jancke, L. (2006). Neural Correlate of Spatial Presence in an Arousing and Noninteractive Virtual Reality: An EEG and Psychophysiology Study. *Cyberpsychol Behav., 9*(1), 30-45.

Beeli, G., Esslen, M., & Jancke, L. (2005). Synaesthesia: when coloured sounds taste sweet. *Nature, 434*(7029), 38.

Beeli, G., Esslen, M., & Jancke, L. (2007). Time Course of Neural Activity Correlated with Colored-Hearing Synesthesia. *Cereb. Cortex*.

Beeli, G., Esslen, M., & Jäncke, L. (2007). Frequency Correlates in Grapheme-Color Synaesthesia. *Psychological Science, 18*(9), 5.

Bindman, L. J., Lippold, O. C. J., & Redfearn, J. W. T. (1964). The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. *J Physiol, 172*(3), 369-382.

Crick, F. C., & Koch, C. (2005). Review. What is the function of the claustrum? *Philosophical Transactions of the Royal Society B: Biological Sciences, 360*(1458), 1271-1279.

Cytowic, R. (1989). *Synesthesia: a Union of the Senses*. New York: Springer.

Deshmukh, V. D. (2006). Neuroscience of Meditation. *TheScientificWorldJOURNAL, 6*, 2239-2253.

Dixon, M. J., Smilek, D., Cudahy, C., & Merikle, P. M. (2000). Five plus two equals yellow. *Nature, 406*(6794), 365-365.

Elbert, T., Lutzenberger, W., Rockstroh, B., & Birbaumer, N. (1981). The influence of low-level transcortical DC-currents on response speed in humans. *Int J Neurosci, 14*(1-2), 101-114.

Fregni, F., Boggio, P., Santos, M., Lima, M., Vieira, A., Rigonatti, S., et al. (2006). Noninvasive cortical stimulation with transcranial direct current stimulation in Parkinson's disease. *Movement Disorders, 21*(10), 1693-1702.

Fregni, F., Boggio, P. S., Lima, M. C., Ferreira, M. J. L., Wagner, T., Rigonatti, S. P., et al. (2006). A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. *Pain, 122*(1-2), 197-209.

Fregni, F., Otachi, P., Do Valle, A., Boggio, P. S., Thut, G., Rigonatti, S. P., et al. (2006). A randomized clinical trial of repetitive transcranial magnetic stimulation in patients with refractory epilepsy. *Annals of Neurology, 60*(4), 447-455.

Hubbard, E. M., & Ramachandran, V. S. (2005). Neurocognitive Mechanisms of Synesthesia. *Neuron, 48*(3), 509-520.

Hummel, F., Voller, B., Celnik, P., Floel, A., Giraux, P., Gerloff, C., et al. (2006). Effects of brain polarization on reaction times and pinch force in chronic stroke. *BMC Neuroscience, 7*(1), 73.

Nitsche, M. A., & Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology, 57*(10), 1899-1901.

North, M., North, S., & Coble, J. (1998). Virtual reality therapy: an effective treatment for phobias. *Stud Health Technol Inform, 58*, 112-119.

Nunn, J. A., Gregory, L. J., Brammer, M., Williams, S. C., Parslow, D. M., Morgan, M. J., et al. (2002). Functional magnetic resonance imaging of synesthesia: activation of V4/V8 by spoken words. *Nat. Neurosci., 5*(4), 371-375.

Paulesu, E., Harrison, J., Baron-Cohen, S., Watson, J. D., Goldstein, L., Heather, J., et al. (1995). The physiology of coloured hearing. A PET activation study of colour-word synaesthesia. *Brain, 118*(3), 661-676.

Purpura, D. P., & McMurtry, J. G. (1965). Intracellular activities and evoked potential changes during polarization of motor cortex. *J Neurophysiol, 28*(1), 166-185.

Ramachandran, V. S., & Hubbard, E. M. (2001). Psychophysical investigations into the neural basis of synaesthesia. *Proc.Biol.Sci., 268*(1470), 979-983.

Rich, A. N., Williams, M. A., Puce, A., Syngeniotis, A., Howard, M. A., McGlone, F., et al. (2006). Neural correlates of imagined and synaesthetic colours. *Neuropsychologia, 44*(14), 2918-2925.

Robertson, L., & Sagiv, N. (2005). *Synesthesia: Perspectives from cognitive Neuroscience*. Oxford: Oxford University Press.

Rothbaum, B., Anderson, P., Zimand, E., Hodges, L., Lang, D., & Wilson, J. (2006). Virtual Reality Exposure Therapy and Standard (in Vivo) Exposure Therapy in the Treatment of Fear of Flying. *Behavior Therapy, 37*(1), 80-90.

Rothbaum, B., Hodges, L., Ready, D., Graap, K., & Alarcon, R. (2001). Virtual reality exposure therapy for Vietnam veterans with posttraumatic stress disorder. *J Clin Psychiatry, 62*(8), 617-622.

Rouw, R., & Scholte, H. S. (2007). Increased structural connectivity in grapheme-color synesthesia. *Nat Neurosci, 10*(6), 792-797.

Sanchez-Vives, M. V., & Slater, M. (2005). From presence to consciousness through virtual reality. *Nat Rev Neurosci, 6*(4), 332-339.

Schiltz, K., Trocha, K., Wieringa, B. M., Emrich, H. M., Johannes, S., & Munte, T. F. (1999). Neurophysiological aspects of synesthetic experience. *J.Neuropsychiatry Clin.Neurosci., 11*(1), 58-65.

Schubert, T., Friedmann, F., & Regenbrecht, H. (2001). The experience of Presence: Factor analytic insights. *Presence: Teleoperator And Virtual Environments, 10*, 266-281.

Shanon, B. (2002). Ayahuasca visualizations: A structural typology. *Journal of Consciousness Studies, 9*(2), 3-30.

Slater, M. (1999). Measuring presence: A response to the Witmer and Singer presence questionnaire. *Presence: Teleoperator And Virtual Environments, 8*(5), 560-565.

Slater, M., Guger, C., Edlinger, G., Leeb, R., Pfurtscheller, G., Antley, A., et al. (2006). Analysis of Physiological Responses to a Social Situation in an Immersive Virtual Environment. *Presence: Teleoperators & Virtual Environments, 15*(5), 553-569.

Slater, M., Pertaub, D., Barker, C., & Clark, D. (2006). An experimental study on fear of public speaking using a virtual environment. *Cyberpsychol Behav., 9*(5), 627-633.

Slater, M., Steed, A., McCarthy, J., & Maringelli, F. (1998). The influence of body movement on subjective presence in virtual environments. *Hum Factors, 40*(3), 469-477.

Smilek, D., Moffatt, B. A., Pasternak, J., White, B. N., Dixon, M. J., & Merikle, P. M. (2002). Synaesthesia: A Case Study of Discordant Monozygotic Twins. *Neurocase, 8*(4), 338-342.

Stroop, J. (1935). Studies of interference in serial verbal reaction. *J Exp Psychol., 18*, 643-662.

Tononi, G., & Edelman, G. M. (1998). Consciousness and Complexity. *Science, 282*(5395), 1846-1851.

Vorderer, P., Wirth, W., Gouveia, F. R., Biocca, F., Saari, T., Jäncke, F., et al. (2004). MEC Spatial Presence Questionnaire (MEC-SPQ): Short documentation and Instructions for Application. Report to the European Community, Project Presence: MEC (IST-2001-37661).

Witmer, B., & Singer, M. (1998). Measuring Presence in Virtual Environments: A Presence Questionnaire. *Presence: Teleoperator And Virtual Environments, 7*(3), 225-240.

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Publications

Beeli, G., Esslen, M., & Jancke, L. (2005). Synaesthesia: when coloured sounds taste sweet. *Nature, 434*(7029), 38.

Beeli, G., Esslen, M., & Jancke, L. (2007). Time Course of Neural Activity Correlated with Colored-Hearing Synesthesia. *Cereb. Cortex*.

Beeli, G., Esslen, M., & Jäncke, L. (2007). Frequency Correlates in Grapheme-Color Synaesthesia. *Psychological Science, 18*(9), 5.

Beeli, G. (2006) «L'oter muond» Siemis, paraulas e legendas en «La müdada» da Clà Biert e lur influenzas junghianas, in : *Annalas da la Società Retorumantscha 119*, 2006, 149-196.